Patient Preference and Adherence

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ORIGINAL RESEARCH

Construction of a three-dimensional model of cardiovascular disease and deployment of a new method of fostering patient adherence to instruction

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Background: For the patient-oriented medical services, it is important to assist the patient in understanding the management of cardiovascular diseases. The strategy of medication instruction is particularly important to enhance medication adherence.

Objective and methods: The original model was newly constructed and covers multiple factors, including those related to renin–angiotensin, metabolism of glucose and lipids, blood coagulation, and the organic basis of the disease. The four factors of cardiovascular diseases and their relationship with the disease state are expressed in the form of a tetrahedral model.

Results and discussion: This disease model illustrates in points, lines, surfaces, and spaces that the factors combine with each other and result in a pathological condition, as determined by the degree of involvement of each factor in a discontinuous manner. The model helps cardiovascular patients to understand visually that there is more than one pathological condition. Our model allowed patients to quickly comprehend the complex pharmacotherapy of cardiovascular diseases by presenting the information in the form of a three-dimensional structure. Lifestyle-related diseases, including cardiovascular diseases, involve complicated factors and require careful pharmacotherapy which is tailored to individual patient needs. In this regard, the development of instructional tools is particularly effective.

Conclusion: The three-dimensional model shows optimum treatment by correctly considering both the quantity and quality of the four pathological factors associated with cardiovascular diseases. Appropriate patient compliance instruction based on life guidance is thought to be essential in the treatment of cardiovascular diseases.

Keywords: medication instruction, patient compliance, adherence to taking medicine, drug information sheet

Introduction

Cardiovascular diseases (CVD) should be generally treated toward prevention and management while, at the same time, maintaining quality of life.[1–4] CVD patients are prescribed a much larger quantity of medicine over a longer period of time compared to most other patients with different conditions. In addition to prescribing appropriate treatment, it is vital to understand the needs of the individual patient. Indeed, patient adherence is especially important for a successful treatment outcome.[5–7]

Patient adherence instruction at pharmacies has mainly focused on explaining individual medicines, but it is somewhat inadequate in helping patients to gain a general understanding of their condition. Various measures aimed at improving patient medication adherence are needed; in particular follow-up by a telephone-based nursing strategy[8] and medications dispensed in time-specific packs or one-dose

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packages at pharmacies.[9] In terms of pharmaceutical improvement, a fixed-dose combination with two or more medications has been developed as part of a risk evaluation and mitigation strategy.[5,10–14] However, good adherence by the patient cannot be assured if he/she is not convinced about the necessity of the prescribed medication. The visual instruction of their medicinal treatment is obviously preferable to assist cardiovascular patients at pharmacies.

To assist cardiovascular patients in this respect, the new CVD model was constructed and covers multiple factors, ie, renin–angiotensin (RA), metabolism of glucose and lipids, blood coagulation, and the organic basis of the disease (Figure 1). The four factors are all vital for life and interact with one another in harmony to maintain proper biological function. We tried to conduct a patient adherence instruction, based on this pathological model, and then carried out a patient questionnaire for assessment by cardiovascular patients.

Method

Drug information and structural model

Creating a pathological model

First, we devised a pathological model. To create a pathological model, we focused on the following four metabolic systems as the main causes of cardiovascular diseases:

1. RA system
2. carbohydrate metabolic system
3. lipid metabolic system
4. blood coagulation system

For example, diseases related to 1, 2, and 3 are pathologies linked to metabolic syndrome, and those related to 2, 3, and 4 are linked to arteriosclerosis and plaque rupture, which are caused by vascular endothelial dysfunction. Diseases related to 1, 2, and 4 include various pathologies induced by insulin resistance, and those related to 1, 3, and 4 are associated with ischemic heart disease and acute coronary syndrome. Cardiovascular diseases are intricately related to 1, 2, 3, and 4. We created a structural model comprising a regular tetrahedron that illustrates the interrelationship between these metabolism systems (Figure 1).

Subject patients

This survey was conducted between April 1, 2009, and November 30, 2011, and involved 1250 patients who were prescribed with cardiovascular drugs (antihypertensive, antianginal, antiarrhythmic, antidiabetic, dyslipidemia, and/or antithrombotic drugs), and who had visited one of the predetermined health insurance pharmacy stores to receive the dispensed medicines. Each patient was instructed using an explanation sheet for medicines, as shown in Figure 2, which includes an example from an actual patient. Moreover, they were instructed using the new three-dimensional model after conventional instruction. A questionnaire was conducted to assess each patient's impression of the instructional method at three Nogami Pharmacy stores in Tokyo, as a cross-sectional study. Patients who could not answer the questionnaire by themselves (eg, due to cognitive impairment) were excluded.

The subject patients were those who had symptoms controlled by outpatient care, were able to self-support their daily life, and had no difficulty swallowing. When the patients

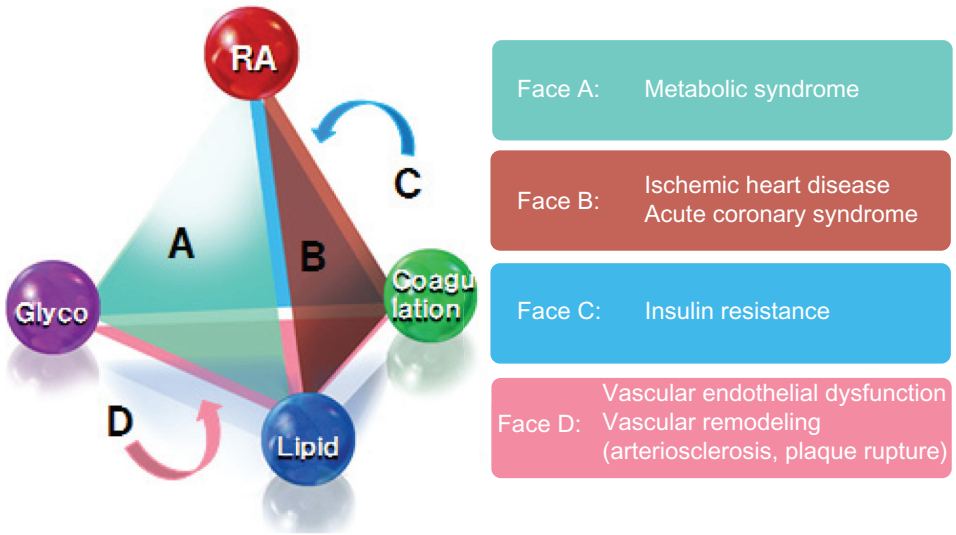

Figure 1 Three-dimensional model of cardiovascular diseases and four pathological factors.
Abbreviations: RA, renin–angiotensin system; glyco, saccharometabolism; lipid, lipid metabolism; coagulation, blood coagulation system.


Patient Name: ○○ ○○

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1. Calslot 10mg (manidipine hydrochloride)

Take two tablets a day, one after breakfast and one after dinner. (Tablets for 30 days)

Medicine to lower blood pressure

Side effects such as dizziness or poor balance (wobbliness) may occur.
If you decide to stop taking medicine without consulting a doctor, your symptoms may worsen.
Taking this medicine with grapefruit juice will boost the medicine's effect.

Consumption of this medicine by pregnant women is usually prohibited.

2. Enalin 5mg (enalapril maleate)

Take two tablets a day, one after breakfast and one after dinner. (Tablets for 30 days)

Medicine to lower blood pressure

Side effects such as dizziness or poor balance (wobbliness) may occur.

Consumption of this medicine by pregnant women and women with child-bearing potential is usually prohibited. Please contact us immediately if you begin to experience symptoms such as coughing, difficulty breathing, shortness of breath, nausea, itching, swelling of the face or tongue, or decrease of urine.

3. Alositol 100mg (allopurinol)

Take one tablet a day after breakfast. (Tablets for 30 days)

Medicine to treat gout and hyperuricemia

Take the tablet with plenty of water.

Please contact us immediately if you begin to experience symptoms such as severe coughing, difficulty breathing, fever, anemia, or bruising.

4. Panaldine 100mg (ticlopidine hydrochloride)

Take two tablets a day, one after breakfast and one after dinner. (Tablets for 30 days)

Medicine to prevent thrombus or improve flow of blood

Consumption of this medicine by persons prone to hemorrhaging is usually prohibited. Please contact us if you experience symptoms such as fever, sore throat, fatigue, or nausea. Persons using this medicine must have their blood tested regularly.

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5. Anplag 100mg (sarpogrelate hydrochloride)

Take two tablets a day, one after breakfast and one after dinner. (Tablets for 30 days)

Medicine to prevent thrombus and control constriction of blood vessels

This medicine is prone to cause bleeding. Please contact us if you experience a nosebleed. Consumption of this medicine by pregnant women, women with child-bearing potential, persons with hemophilia (persons who easily bleed) is usually prohibited.

6. Pramevan 5mg (pravastatin sodium)

Take one tablet a day after dinner. (Tablets for 30 days)

Medicine for hyperlipidemia. Suppresses cholesterol synthesis.

Consumption of this medicine by pregnant women, women with child-bearing potential, or breast-feeding women is usually prohibited. Contact us immediately if you begin to experience any symptoms such as muscle pain, feelings of weakness, fever, coughing, asthma, or difficulty breathing.

7. Amaryl 1mg (glimepiride)

Take one tablet a day after breakfast. (Tablets for 30 days)

Medicine to lower blood glucose. Used for the treatment of diabetes.

If your blood glucose gets too low, you may feel weak, feel voraciously hungry, or even lose consciousness. Carry sugar with you to prevent this problem.

Consumption of this medicine by pregnant women and women with child-bearing potential is usually prohibited.

8. Glactiv 50mg (sitagliptin phosphate hydrate)

Take one tablet a day after breakfast. (Tablets for 30 days)

Medicine to lower blood glucose. Used for the treatment of diabetes.

If your blood glucose gets too low, you may feel weak, feel voraciously hungry, or even lose consciousness. Carry sugar with you to prevent this problem.

Figure 2 Conventional drug sheet for dosing instructions on a patient's prescription.
Note: This is the medicine information for the drug name, photographic image of a tablet, dosage, main efficacy, main side effect, and notice, of each drug.

received the medicines from the pharmacist, each patient was also given patient adherence instruction, which utilized the drug information sheet and this disease treatment model. Each patient voluntarily filled in the anonymous questionnaire (Table 1) and dropped the completed answer sheet into a questionnaire collection box. The consent of the patients was secured by their voluntary actions of filling in the sheets and dropping the sheets into the box. The answer sheets were later shredded in front of two or more staff members to ensure the protection of personal information.

During the course of this study, the Guidelines for Proper Handling of Personal Information by Medical Care/Nursing Care Service Providers and the Ethical Guidelines for Epidemiology Research from the Ministry of Health, Labour, and Welfare in Japan were rigorously followed. While conducting the questionnaire, the objectives of the survey and the handling of the information were fully explained to the patients. The patient adherence instruction using this model was only given to those patients who consented to participate in the study.

The patient adherence instruction using the three-dimensional model by a pharmacist took about 15 minutes to complete. At each store, one pharmacist was in charge of giving instructions for a total of three pharmacists in three different pharmacy stores. Before delivering the instructions based on the three-dimensional model, a meeting was arranged with each nominated pharmacist to ensure the instructional method was standardized. The meeting included role-play simulation.

Answer sheets were handed to each patient during the patient adherence instructional session after which the pharmacist had entered the relevant number of prescribed cardiovascular drugs. Each patient was given the option to complete and return the sheet.

Questionnaire

The following questions were asked:

1. age and sex of the patient;
2. medical history;
3. whether the patient has taken all the prescribed medicines;
4. impression on conventional patient adherence instruction (including drug information sheets);
5. impression of the patient adherence instructions using the three-dimensional model; and
6. to those who answered Question 5 in Table 1 "it was easy to understand," whether the instructions helped motivate them to take the medicines.

Table 1 Patient survey on taking medicines

[Questionnaire on taking medicine] ( )← Number of prescribed medicines
(This questionnaire is for improving patient compliance instruction. The answers will be totalized today, and this sheet will be shredded in the presence of two or more persons.)
This is an anonymous questionnaire. Enter or circle the applicable answers.

1. **Age and sex**
   (Age: in my _____s), (male/female)
2. **Medical history**
   Have you ever contracted a serious disease?
   - No
   - Yes Name of the disease ( )
3. **Taking medicines**
   Do you find some medicines remaining?
   - Never. I have never found medicines remaining or short.
   - Some medicines happen to remain.
   - I intentionally do not take some medicines.
4. **Impression on conventional patient adherence instruction (including drug information sheets)**
   - I can check the information of the medicines at home.
   - Notes about the effects and side effects of the medicines are useful.
   - Other ( )
5. **Impression on the patient adherence instruction using the three-dimensional model**
   - It was easy to understand.
   - I did not understand it very well.
   - Other ( )
6. **If you answered "It was easy to understand" in Question 5, please answer the following question.**
   Did you get a better understanding about taking the medicines and/or do you feel more motivated in treating the disease?
   - I will take the medicines appropriately as I have always taken them.
   - I feel more convinced in taking the medicines.
   - No change.

The questionnaire that asked these questions was presented and assessed at the 2010 Conference of the Japanese Society of Pharmaceutical Health Care and Sciences (held in Nagasaki). The poor adherence was assumed by the pill number on the patient's declaration in this study, although medication adherence should be assessed by drug concentration in blood. The questionnaire sheet is shown in Table 1.

Patient adherence instruction

Conventional patient adherence instruction involves explaining the major effects and side effects of the medication, based on drug information and clear instructions on how to take the medicines. In the new patient adherence instruction, the intention of the pharmacotherapy is briefly explained using the three-dimensional model after the conventional instruction.

For example, this patient in the survey was prescribed eight different medicines. The pharmacist explained the major effects, side effects, and then the necessary precautions for each medicine by presenting the relevant drug information sheets (Figure 2).

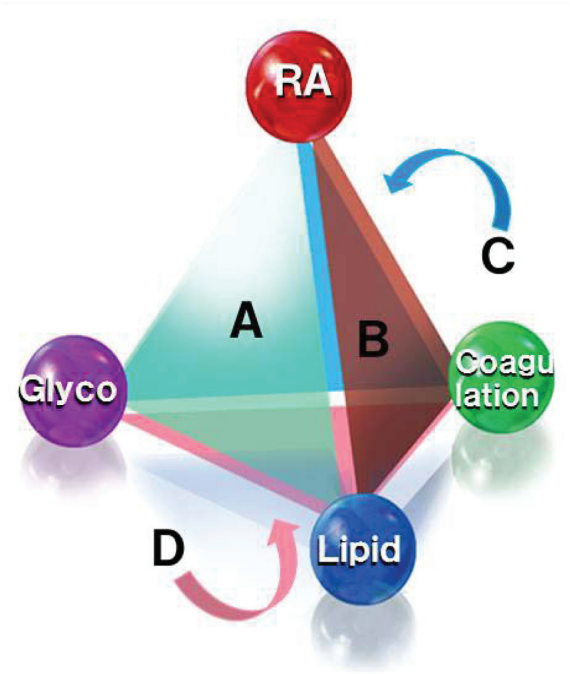
In the new instruction that used the three-dimensional model, it was much easier to outline the intended purpose of the prescribed medication (Figure 3). Specifically, it was explained that the effects of the prescribed medicines (right, Figure 3) corresponded to the apices of the structural model, which helped the patient visualize the relationship between the efficacy of each medicine and the disease. Moreover, the pharmacist was able to explain that the medicines would maintain the tetrahedral structure of the disease model and, thereby, control the onset of cardiovascular disease.

Statistical analysis

Statistical analysis was performed using analysis of variance followed by the post hoc Dunnett's *t*-test for comparing each group. A probability value of $P < 0.05$ was considered statistically significant.

Results

In total, 766 patients answered the questionnaire; 64.4% were male and 35.4% were female (0.2% gave no answer). Patients in their 40s accounted for 1.7% of all respondents; 9.3%, in their 50s; 26.1%, in their 60s; 36.9%, in their 70s; and 26.0% were in their 80s or older. The most frequent number of cardiovascular medicines prescribed per patient was four to six (62.9% of 766 respondents), followed by



Prescription

Patient	Name	KM		Medical institutions or facilities
	Date of birth	Day/month/year	Male/female	Physician name
Date of issuance		20/October/2010		
Valid period of prescription		Day/month/year		Submit to a pharmacy (recognized under the national health insurance system) within four (4) days (unless otherwise specified)
Prescription	[Internal use]	Calslot 10 mg (manidipine hydrochloride) Take two tablets a day, one after breakfast and one after dinner.	2 tablets	Tablets for 30 days
		Panaldine 100 mg (ticlopidine hydrochloride) Anplag 100 mg (sarpogrelate hydrochloride) Take two tablets a day, one after breakfast and one after dinner.	2 tablets 2 tablets	Tablets for 30 days
		Alositol 100mg (allopurinol) Take one tablet a day after breakfast.	1 tablet	Tablets for 30 days
		Pramevan 5 mg (pravastatin sodium) Take one tablet a day after dinner	2 tablets	Tablets for 30 days
		Enalin 5 mg (enalapril maleate) Take two tablets a day, one after breakfast and one after dinner.	2 tablets	Tablets for 30 days
		Amaryl 1 mg (glimepiride) Glactiv 50 mg (sitagliptin phosphate hydrate) Take one tablet a day after breakfast.	1 tablet 1 tablet	Tablets for 30 days
		* Remainder of page intentionally left blank.		
Remarks				

Figure 3 Patient compliance instruction, using the three-dimensional model and an example of a prescription.
Notes: From top to bottom, the medicines prescribed are: calcium antagonist; anticoagulant agent; antipodagric drug; lipid-lowering drug; ACE inhibitor and antidiabetic drug; respectively. Enalin (generic name, enalapril maleate) acts on the RA system. Amaryl (glimepiride) and Glactiv (sitagliptin phosphate hydrate) improve the glycometabolism. Pramevan (pravastatin sodium) improves lipid metabolism. These medicines control metabolic syndrome of Face A. Enalin, Pramevan, and Panaldine (ticlopidine hydrochloride) and Anplag (sarpogrelate hydrochloride) control the onset of ischemic heart disease and acute coronary syndrome on Face B. Calcium antagonist also contributes to control Face B. Cardiovascular diseases on the other faces are controlled in a similar manner. It can be explained that the onset of cardiovascular disease is prevented by controlling the various factors depicted in the tetrahedron with drugs.
Abbreviations: ACE, angiotensin-converting enzyme inhibitor; RA, renin–angiotensin system; glyco, saccharometabolism; lipid, lipid metabolism; coagulation, blood coagulation system.

three or fewer (26.1% of respondents), and seven or more (11.0% of respondents) (Figure 4). For patients in their 50s or younger, the most frequent number of cardiovascular medicines prescribed per patient was four to six (83.3% of this age group), followed by three or fewer (16.7%). For those in their 60s, the highest number was four to six (58.8% of the age group), followed by three or fewer (22.5%), and seven or more (18.7%). For those in their 70s, the most was four to six (62.5%), followed by three or fewer (32.3%), and seven or more (5.2%). For those in their 80s or older, the most frequent number of cardiovascular medicines was four to six (74.9% of this group), followed by three or fewer (18.6%), and seven or more (6.5% for this older group).

Next, we investigated the relationship between medication adherence and the number of prescribed medicines. Of the respondents, 6.2% replied that some cardiovascular medicines "remain;" 33.0% answered that some cardiovascular medicines "remain sometimes;" and 59.0% answered that medicines "never remain," (a further 1.8% gave no answer), as shown in Figure 4. Of the patients to whom three or fewer medicines were prescribed, 25.5% had poor adherence, and 74.5% showed high adherence. Of the patients prescribed with four to six different medicines, 46.3% had poor adherence, and 53.7% showed high adherence. Of those prescribed with seven or more different medicines, 34.6% had poor adherence, and 65.4% showed high adherence (Figure 5).

The largest age group to take medicines related to cardiovascular diseases was the 70–79 year-old patients, followed by the 60–69 year-old age group, and then the 80 and older patients. Low adherence to taking medicine was observed in patients in their 60s–70s who were taking four to six different medicines. Elderly patients in their 80s (13 patients), who were taking seven or more different medicines, showed unexpectedly high adherence while 7.7% had poor adherence.

The patient adherence instruction using the three-dimensional model and drug information sheet was assessed to be easy to understand by 89.9% of the respondents. Furthermore, 61% of them answered they took the medicines while feeling at ease. Taking into account that the respondents stated that they were able to take the medicines as before, 81.6% of the patients evaluated acknowledged that the patient

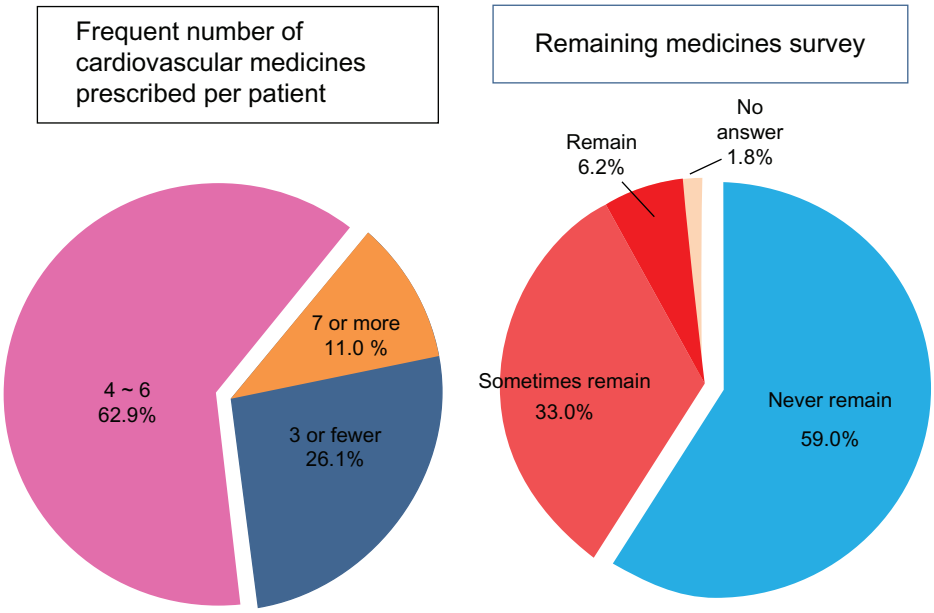


Figure 4 Frequent number of cardiovascular medicines prescribed per patient and survey of the medicines remaining untaken.
Notes: The most frequent number of cardiovascular medicines prescribed per patient was four to six (62.9% of 766 respondents), followed by three or fewer (26.1% of respondents), and seven or more (11.0% of respondents). Of the respondents, 6.2% replied that some cardiovascular medicines "remain," 33.0% answered that some cardiovascular medicines "remain sometimes," and 59.0% answered that medicines "never remain." Another 1.8% gave no answer.

compliance instruction were more effective, as shown in Figure 6. Improved awareness of the disease by reference to this model markedly increased adherence.

Discussion

For the patient-oriented medical services, it is important to assist the patient in understanding the management of cardiovascular diseases. Cardiovascular patients are generally prescribed a much larger quantity of medicine over a longer period of time, compared to most other patients with different conditions. Hence, the medication adherence instruction is particularly important for the patients to understand.

Generally, medication adherence has been reported to display an inverse relationship with the number of prescribed medicines[15] and the increasing age of the patient.[9] In this study, patients prescribed four to six different medicines showed 46.3% poor adherence, while those prescribed seven or more different medicines had a lower rate of poor adherence, ie, 34.6% ($P < 0.05$). Elderly patients who were taking at least seven different medicines showed an unexpectedly high adherence as mentioned above, observantly because they had experienced infarction, heart stroke, and/or pain, and/or feared aggravation. Possible causes for low adherence include insufficient understanding of the disease and/or subjective symptoms. Our findings suggest that medication adherence is not necessarily linked to either the age of the ambulatory patients or the number of prescription medications.

Various measures are needed to improve patient medication adherence, particularly in relation to cardiovascular diseases. To achieve good adherence, it is necessary to convince the patient about the necessity of their medication. Many intervention strategies have been used to improve medication adherence in patients.[8,18] A comprehensive pharmacy care program with the use of one-dose packages led to an increase in good adherence of medications.[9] Fixed-dose combinations have been developed,[5,10–14] such as antihyperglycemic agent or calcium-channel antagonist and β-hydroxy-β-methylglutaryl-CoA (HMG-CoA) reductase inhibitor, to limit the effect of lifestyle-related diseases, such as diabetes, hyperlipidemia, and hypertension. Indeed, fixed-dose combinations with five different medications have been developed in India.[14] However, the safety and efficacy of such fixed-dose medications is unclear, at least in Japan.

Cardiovascular patients are prescribed a wide range of different medicines. In the pharmacy, these medications are dispensed in one-dose packages and in time-specific packs to prevent a failure of patient adherence, as in osteoporosis or rheumatic disorders. Unfortunately, currently the policy in Japan regarding withdrawal of a medicine from the one-dose package is left to the discretion of the patient. Medication nonadherence was reported as a costly problem.[6,9,16,17] Since the cost of medication is paid on the national health insurance system in Japan, this action is not a costly problem. However, this action may have unintended consequences.

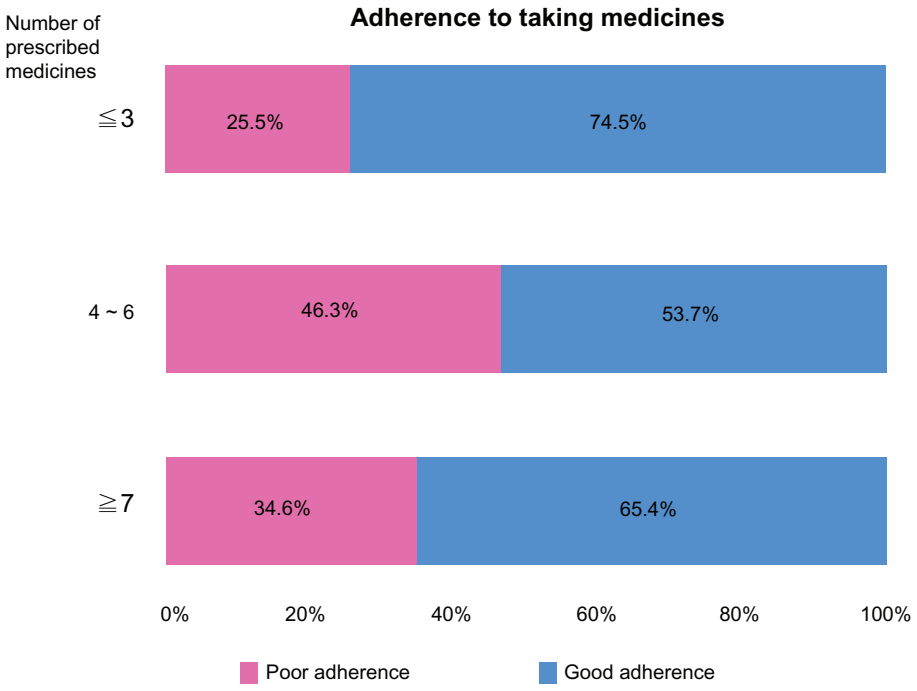


Figure 5 Adherence to taking medicines and the number of medicines prescribed to cardiovascular disease patients.
Notes: For the patients who were prescribed three or fewer medicines, 25.5% had poor adherence, and 74.5% showed high adherence. Of the patients prescribed four to six different medicines, 46.3% had poor adherence, and 53.7% showed high adherence. Of those prescribed with seven or more different medicines, 34.6% had poor adherence, and 65.4% showed high adherence.

For the example of the individual interviews in this study, if the low-density lipoprotein value reaches the normal level during the treatment of cardiovascular disease, the HMG-CoA reductase inhibitor might not be taken for fear of the side effects, which would be an incorrect decision. Indeed, a lack of understanding of the disease and a subjective assessment of the associated symptoms by the patient is a leading factor for poor adherence. To improve medication adherence, a deeper insight into the disease and the drug therapy itself is required by the patient.

Our three-dimensional model shows a variety of factors and resultant pathological conditions that change successively, depending on the degree of involvement of each factor. These complex changes are depicted as points, lines, surfaces, and spaces in the model. The model helped patients to understand visually that cardiovascular diseases comprise

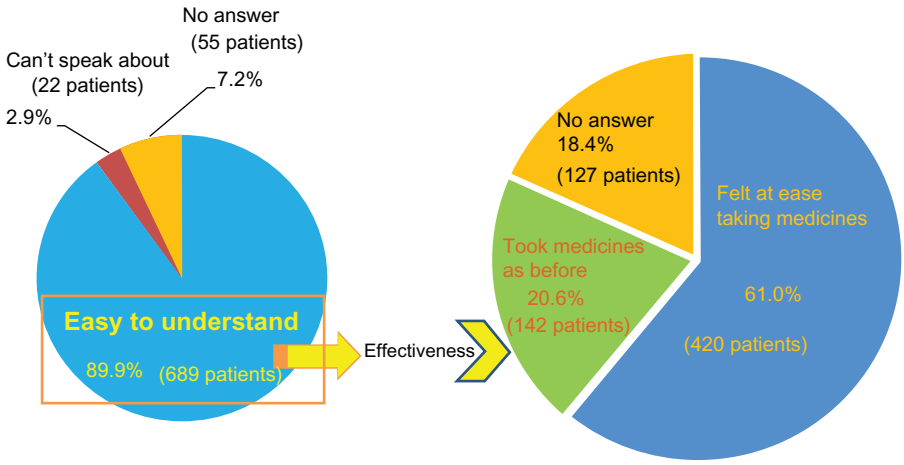


Figure 6 Assessment of the patient to medication instruction using the three-dimensional model for cardiovascular disease.
Notes: The patient compliance instruction using this model was assessed to be easy to understand by 689 patients of 766 respondents. As a result of this instruction, 81.6% of the patients indicated that using the three-dimensional model was more effective at increasing medication adherence.

more than one pathological condition. Indeed, there are four main factors involved in the onset of cardiovascular disease. The four major factors are indispensable to life and to maintain biological function. The model suggests that an imbalance in these factors may lead to the onset of various cardiovascular diseases with the risk of developing into cerebrovascular diseases, heart disease, and, finally, heart failure.

A limitation of this study was the lack of assessment of cure effectiveness and also some factors consistently related to pharmacological efficacy. However, pharmacotherapy of cardiovascular diseases is based on the pleiotropic effects[19,20] of medicines. The three-dimensional model shows optimum treatment by correctly considering both the quantity and quality of the various complex factors. Appropriate patient adherence instruction based on life guidance is likely to be essential in the treatment of CVD.[5–9]

In summary, the patient adherence instruction using this model was assessed to be easy to understand by 689 patients out of 766 respondents. Moreover, 81.6% of the patients stated that using our three-dimensional model increased their medication adherence. Optimum prescription and appropriate patient adherence instruction, based on life guidance, are important for achieving a successful therapeutic outcome. In this regard, the development of instructional tools is particularly effective.

Conclusion

The three-dimensional model shows optimum treatment by correctly considering both the quantity and quality of the four pathological factors associated with cardiovascular diseases. This model should be a useful tool for a medication instruction by the physician and also the pharmacist. The visualization of the relationship between the efficacy of each medicine and the disease would be helpful surely to assist the patient in understanding the pharmacotherapy and medication adherence.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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